

P07 43453 (18810-80645)

AMENDMENT

A Version With Markings to Show Changes Made follows Applicant's Remarks.
Deletions are indicated with bold brackets to distinguish them from brackets that are part of the desired text.

In the Specification:

Please delete the paragraph at page 4, lines 6-11, and insert therefor the following:

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--Intracarotid infusion of leukotriene C.sub.4 (LTC₄) selectively increases the permeability in brain tumor capillaries without affecting the permeability in normal brain capillaries. The effect of LTC₄ on brain tumor capillaries is, however, limited to small molecules and it can only slightly increase the permeability of those small molecules in abnormal brain tissue relative to normal. Accordingly, LTC₄ does not significantly increase the delivery of some larger water soluble molecules to brain tumors or other abnormalities.--

Please delete the paragraph at page 4, lines 12-28, and insert therefor the following:

--The vasoactive nonopeptide bradykinin and agonists or polypeptide analogs thereof (e.g., receptor-mediated permeabilizers [RMPs]) have been injected intravenously to increase blood-brain barrier permeability to co-administered neuropharmaceutical or diagnostic agents.

E2 (B. Malfroy-Camine, *Method for increasing blood-brain barrier permeability by administering a bradykinin agonist of blood-brain barrier permeability*, U.S. Patent No. 5,112,596; J.W. Kozarich *et al.*, *Increasing blood brain barrier permeability with permeabilizer peptides*, U.S. Patent No. 5,268,164). Intracarotid infusion of bradykinin will selectively increase permeability 2- to 12-fold in brain tumor and ischemic brain capillaries for molecules ranging in molecular weight from 100 to 70,000 Daltons (Inamura, T. *et al.*, Bradykinin selectively opens blood-

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tumor barrier in experimental brain tumors, J. Cereb. Blood Flow Metab. 14(5):862-70 [1994]).
 Bradykinin does not increase permeability in the normal blood brain barrier except at very high doses. (Wirth, K. *et al.*, *DesArg9-D-Arg[Hyp3,Thi5,D-Tic7,Oic8]bradykinin (desArg10-[Hoe140]) is a potent bradykinin B1 receptor antagonist*, Eur. J. Pharmacol. 205(2):217-18 [1991]). Opening of the blood-tumor barrier by bradykinin is transient, lasting 15 to 20 minutes. (Inamura *et al.* [1994]). After opening of abnormal brain capillaries with bradykinin, the capillaries become refractory to the bradykinin effect for up to 60 minutes. (Inamura *et al.* [1994]).--.

Please delete the paragraph at page 11, lines 4-11, and insert therefor the following:

--However, the potassium channel agonist employed in the inventive methods is one other than the vasodilator bradykinin (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg), or a polypeptide bradykinin analog, such as receptor mediated permeabilizer (RMP)-7 or A7 (e.g., Kozarich *et al.*, U.S. Patent No. 5,268,164 and PCT Application No. WO 92/18529). Other analogs of bradykinin include related peptide structures which exhibit the same properties as bradykinin but have modified amino acids or peptide extensions on either terminal end of the peptide. Examples of bradykinin analogs include [phe⁸ (CH₂-NH) Arg⁹-bradykinin, N-acetyl [phe⁸ (CH₂-NH-Arg⁹) bradykinin and desArg⁹-bradykinin.--.

Please delete the paragraph at page 18, lines 21-25, and insert therefor the following:

--The dose-dependent nature of this increased permeability is demonstrated in Figure 2, which shows that increasing the dose of NS-1619 results in an increase in the unidirectional transfer constant K_i for [¹⁴C]α-aminoisobutyric acid in RG2 glioma capillaries. At higher doses (100 and 110 μg/kg/min) a significant drop in the arterial blood pressure of the rats was observed. The numbers of rats used in each group is shown in parentheses in Figure 2.--.